INTESA SANPAOLO
INNOVATION CENTER

RNA &GENETHERAPY

INDUSTRY TRENDS REPORT
HEALTHCARE, BIOTECH AND PHARMA
RNA TECHNOLOGIES

Finanziato dall'Unione europea NextGenerationEU
Ministero dell'Università e della Ricerca
Italiadomani
PIANO NAZIONALE DI RIPRESA E RESILIENZA
RNA &GENETHERAPY

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EXECUTIVE SUMMARY

Ribonucleic acid or **RNA therapeutics** are rapidly emerging as a novel class of drugs. They offer a simple approach and a range of advantages versus conventional solutions with growth driven by the development of reimbursement to increase accessibility.

On the *demand side*, RNA therapeutics already address multiple indications while rare diseases and cancers form part of the longer-term pipeline. On the *supply side*, stakeholders are sharing best practices and taking co-development approaches which are supporting enhanced bioinformatics.

Overall, the global RNA therapeutics market was valued at $5.2 billion (b) in 2023 and is expected to reach $17.2b by 2027 with a compound growth rate of 35%.

There are three major types of technology; RNA Antisense Oligonucleotides (RNA ASO) is currently the largest with 80% but is losing ground to both RNA Interference (RNAi) and RNA Messenger (mRNA).

RNA ASO are short single-stranded nucleic acids that bind targeted RNA through base pairing and offer promise in combatting neurodegenerative diseases. However, the translation of ASOs into clinical applications has its challenges such as the lack of sufficient biological activity. Ionis Pharmaceuticals (US) is using ASO to address spinal muscular atrophy.

RNAi is a natural mechanism that stops the invasion of external pathogens and which itself breaks down into three groups; small activating RNA enhances gene expression, small interfering RNA is a popular tool for gene inhibition and micro RNA is still under clinical development. Alnylam Pharmaceuticals (US) is using RNAi to combat cardiometabolic, central nervous system and infectious diseases.

mRNA is fundamental to the central dogma of molecular biology with its therapeutic proteins used to target monogenic disorders. It also serves as a novel way to deliver clustered regularly interspaced short palindromic repeats (CRISPR/Cas9), a principal gene editing tool. Translate Bio (US), acquired by Sanofi, is using mRNA to address a range of pulmonary diseases.

Further to RNA ASO, RNAi and mRNA, *RNA aptamers* is emerging as an alternative RNA solution with significant therapeutic potential and an opportunity to compete in the antibody market. TME Pharma, formerly known as Noxxon Pharma (Germany), has launched a technology to generate aptamers and pursue their future development.

In addition to its success in therapeutics, **RNA vaccines** have become a key technology. They differentiate themselves from conventional solutions due to their rapid clinical development cycle and lack of pre-existing immunity against viral vectors. RNA vaccines also benefit from their broad applicability and strong, international governmental support with momentum in the sector given a huge boost during the recent global pandemic.

There are three types of RNA vaccine with mRNA the most mature and the only solution currently with a technology readiness level (TRL) of 9. *mRNA* in particular was a key element of the public health response to COVID-19 and has quickly evolved from a monovalent to a flexible, multivalent platform. BioNTech (Germany) is best known for its breakthrough mRNA vaccine but also works in the areas of therapeutics, cell therapies and antibodies. The company is joined amongst the mRNA leaders by Moderna (US) and CureVac (Germany) which focuses more on rare disease prevention and treatment.

Self-amplifying RNA represent the next generation of RNA vaccines which are able to increase protection with much lower dosages. Here, VaxEquity (UK) is one of several firms globally developing innovative solutions.

Finally, it is hoped that *circular RNA* vaccines will eventually address the limitations of linear RNAs, with more stability and less degradation.

In the meantime, manufacturers of all three types face a common challenge due to the current lack of a well-developed production process. Market players are looking to accelerate manufacture by improving purification systems, leveraging vector designs and using cell-free systems. Moving forwards, they anticipate that digitising bioprocessing will be invaluable.

Beyond manufacturing, the most significant technical restraint to the growth of the RNA therapeutics and vaccine markets is **RNA stability and delivery**.

Much work is underway to improve RNA *stability* through modifications that use binding proteins, modifying enzymes and eraser proteins. In the longer term, circularization offers another promising approach but with a TRL of only 3 it is currently largely the domain of research and start-ups.

Efforts to enable the *delivery* of the technology are focused on introducing lipids which condense with RNA to form nanoparticles. Within this, PEGylation is the most common of half a dozen different approaches. Acuitas Therapeutics (Canada) and Arcturus Therapeutics (US) are both exploring the potential of nucleic acid delivery carriers. However, lipid nanoparticles have a range of limitations, notably a short shelf life.

As a result, the market is innovating with exosomes, polymers and peptides all emerging as potential RNA delivery mechanisms. *Exomes* offer reduced toxicity and are being pioneered, for example, by Evox Therapeutics (UK) while *polymers* provide non-viral vectors and are being explored by Phosphorex (US) and *peptides* target newer haptic tissues and are being developed by Nanogenics (UK).

As stability and delivery improves, market participants are also looking to new formulations such as lyophilization to deliver longevity while it is hoped that novel administration routes such as oral, needle-free and internasal solutions will boost the public's uptake of RNA and vaccines more broadly.

Moving forwards, RNA will become a key enabler of ***companion diagnostics*** which in turn will pave the way for the development of ***precision medicines***.

Oncology is an area of focus with RNA offering an insight into tumour makeup. Here, it also serves as one of many emerging novel biomarkers which allow physicians to accelerate diagnosis and track progression. Strand Therapeutics (US) is, for example, developing mRNA smart therapies for target-specific action against new cancerous cells while Arpeggio Biosciences (US) is leveraging an artificial intelligence-based transcriptomics platform to speed the oncology drug discovery process.

RNA also plays a growing role in diagnosing ***neurological diseases***, notably through the use of emerging "liquid biopsy" approaches while *genetic diseases* will benefit from sophisticated RNA sequencing techniques.

The report explores the emerging **RNA technologies** which are disrupting the development of therapeutics and vaccines across a range of diseases and conditions as well as the way in which these novel solutions are stabilised and delivered. It also examines the long-term global potential for RNA to facilitate the provision of companion diagnostics and therefore to enable the application of truly personalised and precision medicines.

RNA
THERAPEUTICS

Ribonucleic acid (RNA) therapeutics are rapidly emerging as a novel class of drugs

Over recent years, developments in genomic sequencing technology have facilitated the identification of disease-causing gene sequences and variants. This has led to the advent of a novel class of nucleic acid therapeutics, leveraging Deoxyribonucleic acid (DNA) and RNA. As a result, several DNA-based drugs are already on the market and companies are increasingly focusing on other molecules and RNA as potential disease therapeutics for which conventional drugs are either unavailable or do not work efficiently.

RNAs function in different ways.

For instance, RNA messenger, which is examined in greater detail later in this chapter, serves as a genetic information messenger, from DNA to protein synthesis, and as an essential regulatory element for numerous gene expressions by non-coding RNAs (ncRNAs). Research of ncRNAs has created opportunities to develop therapeutics for several diseases for which gene regulation can be controlled using this emerging approach. The ncRNA mechanisms are typically based on small RNA molecules.

They offer a simple approach and a range of advantages vs. conventional solutions …

Small molecule drugs

The pharmaceutical industry is mostly engaged in developing **small molecule drugs** that bind to the specific region of the target protein, such as receptors and enzymes, and interfere with biochemical processes. Small molecule drugs generally act on downstream pathways of disease-causing genes and do not deal with the disease-related mechanisms. Despite several advantages, the success of small molecule drugs is based on finding a suitable binding site, drug polarity, binding affinities and target druggability.

Antibody drugs

Biological drugs such as **antibody drugs** provide several advantages over small molecule drugs including increased half-life, broader targets, wider engineering possibilities and lower toxicities. However, antibodies also suffer from limitations such as complicated pharmacological profiles, higher production costs and limited administration routes.

Nucleic acids drugs

In a similar way to antibodies, **nucleic acids drugs**, including DNA and RNA, are becoming increasingly popular in the pharmaceutical sector. Nucleic acid therapeutics are advantageous over antibodies because they can enter the cell and therefore interfere directly with protein expression. This provides users with better druggability.

RNA as drugs

Using **RNA as drugs** offers several benefits over conventional small molecule drugs and other solutions such as antibodies and DNA or RNA. RNA therapeutics function at least on a par with other types of drugs and have a much wider potential scope of application. RNAs work directly on target genes and their development and production is relatively cheap. The mass development of RNA therapeutics is achievable and, unlike DNA-based therapeutics, RNAs do not risk genomic integration while their delivery is, in principle, much simpler.

… with growth driven by the development of reimbursement to increase accessibility

The roll-out of new reimbursement systems to widen the accessibility of high-cost drugs in countries such as Canada and the United Kingdom (UK) is propelling RNA therapeutics adoption. For example, Spinraza, a medication used in the treatment of spinal muscular atrophy (SMA), is one of the most expensive treatments available, costing more than $750,000 per patient. Greater public payors' coverage for the drug in developed and developing countries could boost its uptake and that of other new therapeutics including RNA.

On the *demand* side, RNA therapeutics already address multiple indications while rare diseases and cancers form part of the longer-term pipeline

The RNA therapeutics pipeline is not restricted to just a few diseases as biopharmaceutical companies target various conditions. Major market participants such as BioNTech, Moderna and CureVac have a diversified focus, including musculoskeletal diseases, immuno-oncology and metabolic diseases.

Cancers and rare diseases represent significant pipeline therapy areas. For cancer, melanoma, breast cancer, liver cancer and non-small cell lung cancer (NSCLC) are the main areas of exploration and investment while cystic fibrosis and Huntington's disease are the core targets for rare diseases.

Over time, the major disease indications for RNA therapeutics have been;

- **2004–2013**, age-related macular degeneration and familial hypercholesterolemia
- **2014–2018**, spinal muscular atrophy, Duchenne muscular dystrophy, hereditary transthyretin-mediated amyloidosis and familial amyloid polyneuropathy
- **2019–2022**, acute hepatic porphyria, familial chylomicronemia syndrome, primary hyperoxaluria type 1 and heterozygous familial hypercholesterolemia

In addition to cancer and rare diseases, it is hoped that RNA will offer a future pathway to treating infectious diseases, neurological disorders, respiratory diseases, metabolic disorders, cardiovascular diseases and musculoskeletal disorders.

Source: Frost & Sullivan

On the *supply side*, stakeholders are sharing best practices and taking co-development approaches which are supporting enhanced bioinformatics

This approach is leading to better access to sequencing data with collaborations accelerating RNA therapeutics development and streamlining access to small molecules.

Selected examples of partnerships include;

COMPANY 1	COMPANY 2	TYPE	IMPACT
Remix Therapeutics	**Janssen Pharmaceutica**	*Strategic collaboration*	Both companies aim to develop small molecule therapeutics using Remix's REMaster drug discovery platform. Remix will receive tiered royalties for resulting products while Janssen will gain exclusive rights to three specific targets in oncology and immunology
Amgen	**Arrakis Therapeutics**	*Research collaboration*	Arrakis will research and identify RNA-targeted small molecule (rSM) binders for a range of disease targets set out by Amgen
Stoke Therapeutics	**Acadia Pharmaceuticals**	*Collaboration*	Acadia engages Stoke to develop RNA drugs against rare and severe genetic neurodevelopmental diseases of the central nervous system (CNS)

PRINCIPAL ABBREVIATIONS

8-oxoG	*8-oxo-7,8-dihydroguanosine*
ac4C	*N4-acetylcytidine*
AD	*Alzheimer disease*
ADPKD	*Autosomal dominant polycystic kidney disease*
AI	*Artificial intelligence*
AMD	*Age-related macular degeneration*
B	*Billion*
BBB	*Blood-brain barrier*
BM-MSC	*Bone marrow-mesenchymal stromal cells*
C	*Centigrade*
CF	*Cystic fibrosis*
cfRNA	*Cell-free RNA*
circRNA	*Circular nucleic acid*
CNS	*Central nervous system*
CNV	*Copy number variant*
CRISPR	*Clustered regularly interspaced short palindromic repeats*
CSF	*Cerebrospinal fluid*
CTC	*Circulating tumour cell*
ctDNA	*Circulating tumour DNA*

DMD	*Duchenne muscular dystrophy*
DNA	*Deoxyribonucleic acid*
eRNA	*Enhancer RNA*
EV	*Extracellular vesicle*
m5C	*5-methylcytidine*
m6A	*N6-methyladenosine*
m6Am	*N6,2'-O-dimethyladenosine*
miRNA	*Micro-RNA*
mRNA	*RNA messenger*
MSI	*Microsatellite instability*
ncRNA	*Non-coding RNAs*
NGS	*Next-generation sequencing*
NSCLC	*Non-small cell lung cancer*
PBGD	*Porphobilinogen deaminase*
PD	*Parkinson's disease*
PEI	*Polyethylenimine*
RISC	*RNA-inducing silencing complex*
RNA	*Ribonucleic acid*

RNA ASO	*RNA antisense oligonucleotides*
RNAi	*RNA interference*
rSM	*RNA-targeted small molecule*
saRNA	*Self-amplifying RNA*
siRNA	*Small interfering RNA*
SMA	*Spinal muscular atrophy*
SNV	*Single nucleotide variant*
TEP	*Tumour-educated platelet*
FCS	*Familial chylomicronaemia syndrome*
HPIV	*Human parainfluenza*
HPV	*Human papillomavirus*
INDEL	*Insertion and deletion*
iNeST	*Individualized neoantigen specific immunotherapy*
IP	*Intellectual property*
LICA	*Ligand-conjugated antisense*
lncRNA	*Long non-coding RNA*
LNP	*Lipid nanoparticle*
tRFs	*tRNA-derived RNA fragments*
TRL	*Technology readiness level*
tRNA	*Transfer RNA*
UK	*United Kingdom*
US	*United States*
UTR	*Untranslated region*
WES	*Whole-exome sequencing*
WGS	*Whole-genome sequencing*
Ψ	*Pseudouridine*

ABOUT INTESA SANPAOLO INNOVATION CENTER:

Intesa Sanpaolo Innovation Center is the company of Intesa Sanpaolo Group dedicated to innovation: it explores and learns new business and research models and acts as a stimulus and engine for the new economy in Italy. The company invests in applied research projects and high potential start-ups, to foster the competitiveness of the Group and its customers and accelerate the development of the circular economy in Italy.

Based in the Turin skyscraper designed by Renzo Piano, with its national and international network of hubs and laboratories, the Innovation Center is an enabler of relations with other stakeholders of the innovation ecosystem - such as tech companies, start-ups, incubators, research centres and universities - and a promoter of new forms of entrepreneurship in accessing venture capital. Intesa Sanpaolo Innovation Center focuses mainly on circular economy, development of the most promising start-ups, venture capital investments of the management company Neva SGR and applied research.

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Published: June 2024